Hyperosmolar Hyperglycaemic State

Synonyms: hyperosmolar hyperglycaemic nonketotic coma (HONK), diabetic nonketotic coma, hyperosmolar nonketotic state, hyperosmolar nonketotic hyperglycaemia (HNKH)

See also separate articles Coma, Diabetes and Intercurrent Illness, Management of Type 2 Diabetes Mellitus, Diabetic Ketoacidosis and Childhood Ketoacidosis.

Hyperosmolar hyperglycaemic state (HHS) occurs in people with type 2 diabetes. Very high blood glucose levels (often over 40 mmol/L) develop as a result of a combination of illness, dehydration and an inability to take normal diabetes medication due to the effect of illness. HHS is characterised by severe hyperglycaemia with marked serum hyperosmolarity, without evidence of significant ketosis. HHS is a potentially life-threatening emergency.

Hyperglycaemia causes an osmotic diuresis with hyperosmolarity leading to an osmotic shift of water into the intravascular compartment, resulting in severe intracellular dehydration. Ketosis does not occur due to the presence of basal insulin secretion sufficient to prevent ketogenesis but insufficient to reduce blood glucose.

A mixed picture of HHS and diabetic ketoacidosis (DKA) may occur. There is no precise definition of HHS but there are characteristic features that differentiate it from other hyperglycaemic states such as DKA. These are:[1]

- Hypovolaemia.
- Marked hyperglycaemia (30 mmol/L or more) without significant hyperketonaemia (<3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L).
- Osmolality usually 320 mosmol/kg or more.

Causative conditions

The following list is not exhaustive but covers the most common causes and those that may be easily overlooked.

### Common and important causes of hyperosmolar hyperglycaemic state (HHS)[2]

<table>
<thead>
<tr>
<th>Intercurrent or co-existing illness</th>
<th>Medication-induced</th>
<th>Diabetes-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Myocardial infarction.</td>
<td>- Metformin during intercurrent illness.</td>
<td>- First presentation of diabetes mellitus:</td>
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<td>- Infection:</td>
<td>- Diuretics (especially thiazide and loop types.).</td>
<td>- Unsuspected</td>
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<td>- Urinary tract infection</td>
<td>- Beta-blockers.</td>
<td>- Undiagnosed</td>
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<td>- Pneumonia</td>
<td>- H2-receptor antagonists.</td>
<td>- Poor diabetic control/non-compliance:</td>
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<td>- Cellulitis</td>
<td>- Diuretics total parenteral nutrition/glucose-containing fluids.</td>
<td>- Intentional</td>
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<td>- Systemic sepsis</td>
<td>- Calcium-channel blockers.</td>
<td>- Accidental</td>
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<td>- Dental infection/abscesses</td>
<td>- Chlorpropamide/other anti-psychotics (eg, olanzapine).</td>
<td>- Self-neglect</td>
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<td>- Stroke/TIA/intracranial haemorrhage.</td>
<td>- Carbonic anhydrase inhibitors (eg, diazoxide).</td>
<td>- Neglect or abuse by carers/family</td>
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<tr>
<td>- Hyperthermia.</td>
<td>- Glucocorticoids (eg, prednisolone, hydrocortisone).</td>
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<tr>
<td>- Hypothermia.</td>
<td>- Phenytoin and other anticonvulsants.</td>
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<td>- Intestinal ischaemia/infarction.</td>
<td>- Substance misuse:</td>
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<td>- Pancreatitis.</td>
<td>- Alcohol</td>
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<td>- Pulmonary embolism.</td>
<td>- Cocaine</td>
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<td>- Acute kidney injury or decompensated chronic kidney disease.</td>
<td>- Amphetamines</td>
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<td>- Any cause of acute abdomen.</td>
<td>- MDMA (ecstasy)</td>
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<td>- Hyperthyroidism.</td>
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<td>- Burns.</td>
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<td>- Cushing's syndrome or ACTH-secreting tumour.</td>
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<td>- Gastrointestinal bleeding.</td>
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</table>

Epidemiology

- The annual incidence in the USA is estimated at less than 1 case per 1,000 person-years but the incidence is likely to increase in line with the increasing prevalence of type 2 diabetes.
- Although typically occurring in the elderly, HHS is presenting in ever-younger adults and teenagers, often as the initial presentation of type 2 diabetes.[1]

Risk factors
It can affect people of all ages but is much more common in those who are older and have type 2 diabetes.
- Nursing/rest home residents or those who live alone.
- Dementia.
- Sedative drugs.
- Heatwaves.
- Propensity to infection - eg, immunosuppressed, corticosteroid users.
- Children with long-term steroid use and gastroenteritis are at increased risk.\[2\]

**Presentation**\[2\]
- HHS usually presents in older patients with type 2 diabetes mellitus. However, HHS has been reported in children, in line with the increasing incidence of obesity and type 2 diabetes in children and adolescents.\[3\] HHS may be the first presentation of type 2 diabetes.
- Patients usually become very ill very quickly and in need of urgent assessment and treatment.
- HHS normally manifests as an extremely ill patient who, on initial assessment, shows signs of gross dehydration and focal or global neurological dysfunction.

**Symptoms**
- Patients usually notice early symptoms of generalised weakness, leg cramps or visual impairment.
- Nausea and vomiting may occur but this is much less so than for DKA.
- As the condition progresses, patients may become bed-bound, confused and lethargic.
- Focal neurological symptoms such as weakness on one side or hemisensory abnormalities may develop and be easily confused with stroke.
- Seizures are present in up to 25% of cases. Seizures may be generalised, focal, movement-induced or myoclonic-jerk type.
- Despite the condition’s name, coma is a relatively rare feature affecting only about 10% of those who present with the relevant metabolic abnormalities. Progression to coma represents severe disease.

**Signs**

**General inspection:**
- Patients usually appear ill and look exhausted.
- There may be evidence of disorientation or confusion.
- Signs of dehydration such as dry mouth, decreased skin turgor or sunken eyes may be visible on general inspection.

**Vital signs:**
- Tachycardia is common due to dehydration.
- Hypotension may be present due to severe fluid depletion or underlying sepsis/cardiac impairment. Postural hypotension is not a specific or sensitive sign due to its high background prevalence in the elderly population.
- An increased respiratory rate may be found due to a compensatory attempt to reduce metabolic acidosis.
- The temperature should ideally be measured using a rectal thermometer and may reveal pyrexia or hypothermia.
- Pulse oximeter measurement may show haemoglobin desaturation (in which case, administer oxygen whilst conducting further assessment).

**Skin:**
- A careful examination of the entire skin surface is needed, looking for rashes and localised sepsis (eg, cellulitis or leg ulcers).
- Turgor will be reduced due to dehydration.
- In patients with infection, the skin may feel warm and moist. Severe sepsis can lead to cold, dry, mottled skin.

**Head:**
- Check the eyes to see if they are sunken.
- Look in the mouth for dryness, check the pharynx for inflammation and perform auroscopy, looking for middle-ear infection.
- A quick screening cranial nerve examination may reveal visual field deficits, nystagmus or other cranial nerve palsies.

**Neck:**
- Check the lymph glands for enlargement and look for goitre due to thyrotoxicosis.
- Check for neck stiffness due to meningitis.

**Chest examination:**
- This may reveal evidence of pneumonia or acute respiratory distress syndrome (a potential complication of HHS).

**Cardiac examination:**
- This may reveal evidence of heart failure as the precipitant illness, or give reason to suspect myocardial infarction or infective endocarditis.
• Abdominal examination:
  • This should look for signs of an acute abdomen.
  • Paralytic ileus or gastroparesis may occur during the acute phase but usually settles when HHS is treated.
  • Persisting signs of intestinal obstruction should prompt a search for an intra-abdominal cause for HHS.
  • Consider rectal examination if there is reason to suspect gastrointestinal bleeding, prostatitis or pelvic abscess.
  • Women may need a pelvic examination/swab to exclude infection in the gynaecological tract.

• Neurological examination:
  • Check orientation and higher cerebral functions.
  • Check Kernig’s sign for possible meningitis.
  • Cranial nerves and limb tone, power, co-ordination, reflexes and sensation should be assessed.

Differential diagnosis

• Once the clinical picture is combined with initial investigation results, the diagnosis is usually clear. The range of precipitating conditions is vast (see table, above).
• Older patients often present with delirium when physically unwell and this is the major differential at first assessment. The same is true of an acute presentation of dementia.
• Some forms of acute poisoning or intentional overdose can produce metabolic derangement and should be considered as a cause, particularly where pre-existing diabetes is not established.
• Lactic acidosis or other causes of metabolic acidosis should be borne in mind, especially where there is a large anion gap (see below for calculation).

Investigations

• Urinalysis shows marked glycosuria with normal or only slightly elevated ketones.
• Capillary glucose should be checked straightaway and is usually markedly elevated at >30 mmol/L. Samples should also be sent for plasma glucose.
• Serum osmolality is usually >320 mmol/L (normal range is 290 ± 5 mmol/L). Osmolarity can be approximately calculated as:
  plasma osmolarity = 2 (Na mmol/L + K mmol/L) + urea mmol/L + glucose mmol/L.
• Renal function tests and electrolytes: dehydration and pre-renal acute kidney injury. Sodium and potassium levels are deranged.
• FBC, CRP.
• Blood cultures, urine cultures and cultures from any other site of possible infection, including lumbar puncture if indicated.
• Arterial blood gases: pH is usually above 7.3. The anion gap is usually within the normal range (see the separate Acid-base Balance and Metabolic Acidosis articles).
• Creatine kinase and cardiac enzymes: myocardial infarction and rhabdomyolysis can cause the syndrome or arise as a complication.
• ECG and CXR.
• Further investigations to detect the underlying cause should include urine, blood and any other relevant cultures, and specific tests directed at detecting the most likely cause in a given case, where relevant to ongoing management - eg, lumbar puncture for suspected meningitis.

Management

The goals of treatment of HHS are to:

• Treat the underlying cause and gradually and safely normalise the osmolality.
• Replace fluid and electrolyte losses.
• Normalise blood glucose.

Other goals include the prevention of potential complications, including arterial or venous thrombosis, cerebral oedema and foot ulceration. [1]

Initial general measures

• Resuscitation: check for and treat any problems with airway, breathing or circulation, to buy time.
• Intubate and ventilate patients with deteriorating oxygen saturations (take senior A&E/medical/anaesthetic advice).
• Obtain large-bore intravenous (IV) access (central line may be needed).
• Connect the patient to an ECG monitor, SaO2 monitor and BP monitor.
• Give oxygen if needed.
• Catheterise the patient to obtain urine and monitor urine output.
• Consider passing a nasogastric tube if there is impaired consciousness and risk of aspiration.
• Consider transfer to a high-dependency area as soon as feasible.
• Alert the acute medical/diabetic team.

Main principles of management [1]

• Measure or calculate osmolality (2Na+ + glucose + urea) frequently to monitor the response to treatment.
- Use IV 0.9% sodium chloride solution as the principal fluid to restore circulating volume and reverse dehydration. Only switch to 0.45% sodium chloride solution if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- The fall in blood glucose should be no more than 5 mmol/L/hour. Low-dose IV insulin (0.05 units/kg/hour) should only be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β-hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+).
- IV fluid replacement aims to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within next 12 hours, though complete normalisation of biochemistry may take up to 72 hours.
- The patient should be encouraged to drink as soon as it is safe to do so and an accurate fluid balance chart should be maintained until IV fluids are no longer required.
- Assessment for complications of treatment - eg, fluid overload, cerebral oedema or central pontine myelinolysis (as indicated by a deteriorating conscious level) - must be undertaken frequently (every 1-2 hours).
- Underlying precipitants must be identified and treated.
- Prophylactic anticoagulation is required in most patients.
- All patients should be assumed to be at high risk of foot ulceration. The heels should be appropriately protected and daily foot checks undertaken.

At all times, if the patient is not improving, senior advice should be sought.

Complications

HHS has a higher mortality than DKA and may be complicated by vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis. Seizures, cerebral oedema and central pontine myelinolysis are uncommon but may also occur.[1]

- Ischaemia or infarction affecting any organ, particularly myocardial infarction and cerebrovascular event.
- Thromboembolic disease, including deep vein thrombosis and pulmonary embolism.
- Acute respiratory distress syndrome.
- Disseminated intravascular coagulation.
- Multi-organ failure.
- Rhabdomyolysis.
- Cerebral oedema.
- Central pontine myelinolysis.
- Iatrogenic complications due to inexpert rehydration and electrolyte management; over-administration of insulin; fluid overload leading to cardiac failure.

Prognosis

Mortality rates have improved in recent years but remain high at 15-20%. [4]

Prevention[2]

- People with diabetes should be well educated about how to manage their condition, particularly when ill.
- Awareness in the medical profession that this is a possible presentation of diabetes may lead to earlier recognition of the problem.
- Patients who have had HHS should receive education and extra support to try to stop this dangerous situation from recurring.

Further reading & references

- Type 2 diabetes in adults: management; NICE Guidelines (December 2015, updated May 2017)
- Management of diabetes; Scottish Intercollegiate Guidelines Network - SIGN (March 2010 - updated Sept 2013)
- Diabetes UK
- Diabetes - type 2; NICE CKS, October 2015 (UK access only)

1. The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes; Joint British Diabetes Societies Inpatient Care Group (August 2012)

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